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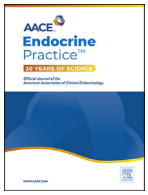

Review Article

Thyroid Emergencies: A Narrative Review

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ABSTRACT

Introduction: Myxedema coma and thyroid storm are rare thyroid emergencies associated with considerable mortality and morbidity.
Results: Myxedema coma is a state of decompensated hypothyroidism with widespread multi-organ dysfunction, including impaired consciousness, mixed respiratory failure, and hypothermia. Thyroid storm is the extreme state of thyrotoxicosis occurring when a patient's metabolic, thermoregulatory, and cardiovascular compensatory mechanisms are surpassed; clinical features include hyperthermia, neuropsychiatric symptoms, and tachyarrhythmias. Thyroid emergencies usually result from a precipitating event or trigger transforming a previously compensated hypothyroid or thyrotoxic state. Supportive care for the cardiovascular, respiratory, and thermoregulatory manifestations, as well as possible intercurrent illness or adrenal insufficiency, plays a lead role in the management. For myxedema coma, treatment typically includes high-dose levothyroxine with the addition of liothyronine for critically ill patients. Management of thyroid storm is multipronged and stepwise, consisting of first-line thionamide and beta-adrenergic receptor antagonist therapy, followed by inorganic iodine, cholestyramine, plasmapheresis, or emergent thyroidectomy in appropriate severely ill patients.
Conclusions: This review provides an updated narrative overview of the diagnosis and management of myxedema coma and thyroid storm.
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Introduction

Thyroid hormone affects almost every cell and organ in the body, extending from its core role in obligatory and facultative thermogenesis to its profound effects on the cardiovascular system. Two thyroid emergencies, myxedema coma (or myxedema crisis)[1] and thyroid storm, lie on opposing ends of a spectrum ranging from thyroid hormone deficiency to excess and are associated with considerable morbidity and mortality. Myxedema coma is a state of decompensated hypothyroidism resulting in widespread multi-organ dysfunction occurring after prolonged, often unrecognized thyroid hypofunction. Myxedema coma's cardinal clinical features are hypothermia and impaired consciousness, ranging from obtundation to coma.[2] Because neither myxedema nor frank coma is always present and neuropsychiatric features including poor memory, cognitive dysfunction, depression, or even psychosis have been observed,[3] myxedema crisis may be a more apt name.[1] Similarly and antithetically, thyroid storm is the extreme state of thyrotoxicosis occurring when the patient's metabolic, thermoregulatory, and cardiovascular compensatory mechanisms are surpassed; high fever and tachyarrhythmia are near universal.[4,5] Early recognition and prompt treatment are crucial to patient survival.

Epidemiology and Prognosis

Recent estimates of the incidence of thyroid storm using population-based data sets examining cases per 100 000 persons/y include 0.20 cases in Japan,[6] a range between 0.57 and 0.76 cases over 10 years in the United States,[7] and 0.55 cases in Taiwan.[8] In France, Bourcier et al[9] found the incidence to be 6.3 per 100 000 intensive care unit (ICU) admissions. In the United States, the incidence of thyroid storm was determined to be 16% to 17% of patients hospitalized with thyrotoxicosis.[7,10] There is a striking

Abbreviations: ATDs, antithyroid drugs; BWPS, Burch-Wartofsky Point Scale; FT4, free thyroxine; ICU, intensive care unit; IV, intravenous; JTA, Japanese Thyroid Association; LT3, liothyronine; LT4, levothyroxine; MMI, methimazole; PTU, propylthiouracil; T3, triiodothyronine; T4, thyroxine; TSH, thyroid stimulating hormone.

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female predominance, likely because the most common cause of thyrotoxicosis is Graves disease, which exhibits a female-to-male ratio between 4 and 10:1.[11] Akamizu et al[6] reported that 77% of the patients who met criteria for definite or suspected thyroid storm were women, and Thiyagarajan et al[12] reported a female-to-male ratio as high as 4.2. Mortality rates in thyroid storm are relatively high, even in recent literature, ranging from 1.2% to 3.6% over a 10-year study period (n = 19 723)[7] from U.S. hospitals, but 17% (n = 92) in a multicenter French ICU-specific database.[9] Other estimates range from 5% to 10.3%.[8,12,13] Galindo et al[7] note a 12-fold higher hospital mortality in thyroid storm compared to thyrotoxicosis without thyroid storm. Studies investigating clinical features that are associated with mortality in thyroid storm are reviewed in Table 1.[6,7,9,14-16]

The incidence of myxedema coma is less than that of thyroid storm. Chen et al[17] estimated the incidence of hospitalization for myxedema coma to be 2.56 cases per 1 million people/y from 2016 to 2018 from the U.S. National Inpatient Sample. Other estimates range from 1.08 per 1 million people/y in Japan from 2010 to 2013[18] to 5.6 cases per 100 000 patients admitted to the ICU in France.[19] A small, single-center study reported an increased incidence of myxedema coma in the 5 years during and after the COVID-19 pandemic thought due to barriers to health care access.[20] The mortality rate for myxedema coma appears to have decreased in recent decades. Single-center studies with samples from 7 to 90 patients from 1991 to 2008 report estimated mortality rates ranging from 28.5% to 52%.[21-24] More recent, larger studies from national inpatient or ICU databases place mortality at 6.8% to 29.5%.[17-19] Studies investigating clinical features that are associated with mortality myxedema coma are reviewed in Table 2.[17-19,22-25]

Highlights

- Myxedema coma and thyroid storm are life-threatening thyroid emergencies that result from decompensation of uncomplicated hypothyroidism and thyrotoxicosis, respectively, usually by a triggering event such as infection and/or sudden change in thyroid hormone. They require prompt recognition and treatment
- Myxedema coma results in multiorgan dysfunction, hypothermia, and impaired consciousness, sometimes with myxedema, and is treated with intensive supportive care and high-dose thyroid hormone replacement therapy
- Thyroid storm manifests as hyperthermia, altered consciousness, gastrointestinal dysfunction, and/or cardiovascular complications including tachyarrhythmias and high-output congestive heart failure; treatment includes intensive supportive care, anti-thyroid drugs, beta-adrenergic receptor blockade, as well as iodine and additional therapies that reduce circulating thyroid hormone amount and action

Clinical Relevance

Myxedema coma and thyroid storm are rare thyroid emergencies with high mortality, requiring evidence of clinical decompensation in the setting of hypothyroidism or thyrotoxicosis for diagnosis. Urgent recognition, intensive supportive care, and rapid initiation of disease-specific therapy by a multidisciplinary team are critical for optimal outcomes.

Precipitating Factors

Thyroid storm and myxedema coma share a common pattern of often being precipitated by an incipient triggering event and/or a sudden change in thyroid hormone level, which causes a pathophysiologic cascade that transforms compensated, long-standing hypothyroidism or thyrotoxicosis into a decompensated state. Although the exact mechanism is incompletely understood and varies by trigger, it is generally thought to be due to

Table 1
Clinical Factors Associated With or Predictive of Mortality in Patients With Thyroid Storm

Study authors and year	Study design and methods	Sample size	Overall mortality rate	Factors associated with or predictive of mortality
Akamizu et al[6] 2012	Retrospective observational study Logistic regression analysis or multiple regression analysis with the stepwise method	356	10.7%	1. Shock 2. Disseminated intravascular coagulation 3. Multiple organ failure
Swee et al[14] 2015	Retrospective case series Fisher exact test	28	25%	1. Central nervous system involvement of moderate severity based on the Burch-Wartofsky Point Scale (delirium, psychosis, and extreme lethargy)
Ono et al[15] 2016	Retrospective observational study Multivariable logistic regression analysis	1324	10%	1. Age of >60 y 2. Higher Japan Coma Scale score at admission 3. Nonuse of antithyroid drugs and beta-blockade during admission 4. Requirement for mechanical ventilation and therapeutic plasma exchange combined with hemodialysis
Galindo et al[7] 2019	Retrospective longitudinal analysis Multivariate analyses based on design-adjusted logistic regression	19 723	1.2%-3.6%	1. Elderly patients (>65 y) 2. Charlson Comorbidity Index score of ≥3
Bourcier et al[9] 2020	Retrospective multicenter observational study Bivariate analyses followed by a multivariable model Multiple backward-stepwise logistic regression analyses	92	17%	1. SOFA score without cardiovascular component 2. Cardiogenic shock within 48 h after ICU admission
Furukawa et al[16] 2024	Prospective multicenter registry-based study Multivariate logistic regression analysis	110	5.5%	1. Lower BMI 2. Shock 3. Lack of fever ≥38 °C 4. LVEF <44%

Abbreviations: BMI = body mass index; ICU = intensive care unit; LVEF = left ventricular ejection fraction; SOFA = Sequential Organ Failure Assessment.

Table 2
Clinical Factors Associated With or Predictive of Mortality in Patients With Myxedema Coma

Study authors and year	Study design and methods	Sample size	Overall mortality rate	Factors associated with or predictive of mortality
Hylander and Rosenqvist[25] 1985	Retrospective case series *t* test	11	64%	1. Older age 2. Lower initial heart rate 3. Higher estimated T3 serum levels following replacement therapy with T4 and T3
Yamamoto et al[22] 1999	Retrospective case series and literature review Multiple logistic regression analysis	87 (5 patients and 82 cases from the literature)	31%	1. Greater age 2. Cardiac complications 3. Treatment with high-dose T4 (≥500 mcg/d) 4. Treatment with high-dose T3 (≥75 mcg/d)
Rodríguez et al[23] 2004	Randomized controlled trial (unblinded) *t* test χ^2 test or Fisher exact test	11	36.4%	1. Comatose on admission 2. Lower GCS score 3. Higher APACHE II score
Dutta et al[24] 2008	Prospective observational study Multiple linear regression model	23	52%	1. Hypotension and bradycardia at presentation 2. Need for mechanical ventilation 3. Hypothermia unresponsive to treatment 4. Sepsis 5. Stoppage of L-T4 treatment 6. Intake of sedative drugs 7. Lower GCS score 8. Higher APACHE II score 9. Higher SOFA score
Ono et al[18] 2017	Retrospective observational study χ^2 test Multivariable logistic regression analysis	149	29.5%	χ^2 test results: 1. Use of steroids and catecholamines 2. Requiring mechanical ventilation Multivariable logistic regression analysis results: 1. Higher age 2. Use of catecholamines (with or without steroids)
Bourcier et al[19] 2023	Retrospective multicenter observational study Bivariate analyses Multiple backward-stepwise logistic regression analyses to select the final regression model	82	26%	1. Age of >70 y 2. Hemodynamic failure (defined as an SOFA score cardiovascular component of ≥2) 3. Ventilation impairment (defined as an SOFA score ventilation component of ≥2)
Chen et al[17] 2024	Retrospective observational study Multivariable logistic regression analysis	2495	6.8%	1. Age of >65 y compared with 18-40 y 2. Large hospital size 3. Charlson Comorbidity Index score of >0 4. Cardiogenic shock 5. Cardiac arrest 6. Acute renal failure 7. Septicemia

Abbreviations: APACHE II = Acute Physiology and Chronic Health Evaluation II; GCS = Glasgow Coma Scale; SOFA = Sequential Organ Failure Assessment; T4 = thyroxine; T3 = triiodothyronine.

unavailability of usually inducible systems, which are constitutively activated in chronic hypothyroidism or thyrotoxicosis to maintain homeostasis, reducing capacity to respond to a new acute insult.[4,26] A list of reported triggers for myxedema coma and thyroid storm are represented in Figure 1.[1,3-5,23,24,27-29] Cold exposure is worth explicitly mentioning: 40% of myxedema coma ICU admissions were in the winter season in a large, multicenter, retrospective study. Cold exposure can quickly lead to hypothermia in the essentially poikilothermic hypothyroid patient. In physician-completed surveys of 356 patients with thyroid storm, Akamizu et al[6] reported that 70% of patients with suspected or definite thyroid storm had an identifiable trigger, with irregular use or discontinuation of anti-thyroid drugs (ATDs) and infection being the most common. In the same study, thyroid surgery, once a commonly reported precipitant of thyroid storm, was not identified thought due to improvements in preoperative preparation and increased use of radioactive iodine therapy.[30]

Myxedema Coma

Pathogenesis and Clinical Features

The pathophysiology of myxedema coma is complex, encompassing nearly every organ system, but also simple, in that all organ dysfunction stems from low intracellular triiodothyronine (T3). The pathognomonic finding is myxedema, the disordered accumulation of hyaluronic acid and other glycosaminoglycans in the interstitium of the skin, intestine, lung, muscles (including the myocardium), and renal medulla. Myxedema causes interstitial edema, effusions, and organ dysfunction as the increased hyaluronate content leads to mechanical and neural transmission defects.[31] The accumulation of glycosaminoglycans is due to the lack of thyroid hormone–mediated inhibition of fibroblast synthesis of hyaluronate, fibronectin, and collagen; therefore, resolution of myxedema requires thyroid hormone.[32] Hypothermia is another hallmark because as much as 30% of obligatory thermogenesis depends on thyroid hormone; it has been aptly stated that "if there is a single hallmark of impending shock and coma, it is the appearance and progression of hypothermia."[33,34]

Significantly depressed hypoxic and hypercapnic ventilatory drive has been shown, even in patients without underlying obstructive lung disease.[35] Pleural effusions, obesity, macroglossia, myxedematous swelling of the upper airway, diaphragmatic and respiratory muscle weakness, and/or concomitant pneumonia or aspiration pneumonitis lead to respiratory failure, which is, historically, the most common cause of death.[1] Cardiac function is depressed: impaired chronotropy, inotropy, and diastolic function, along with increased systemic vascular resistance, create an

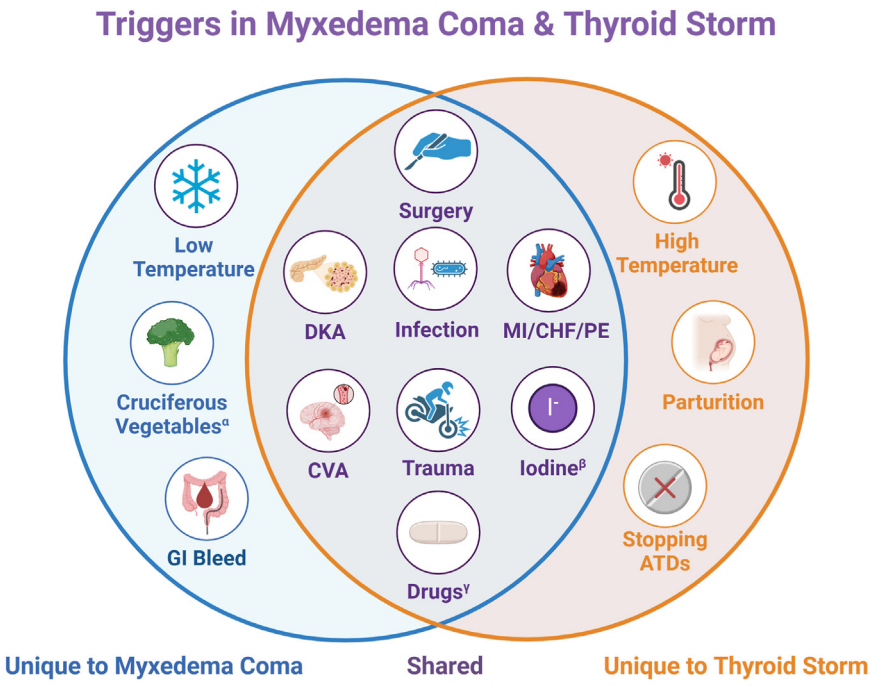

Fig. 1. Triggering mechanisms that may lead to decompensation of uncomplicated hypothyroidism and thyrotoxicosis.[1,3-5,23,24,27,28] α, Less than 1.5 kg daily, due to thyroid-inhibiting glucosinolates.[29] β, Most often from iodinated contrast or amiodarone. γ, Drugs reported to trigger myxedema coma (sedatives, narcotics, amiodarone, and lithium), thyroid storm (salicylates and pseudoephedrine), and both (anesthetics). *ATD* = antithyroid drug; *CHF* = congestive heart failure; *CVA* = cerebrovascular accident; *DKA* = diabetic ketoacidosis; *GI* = gastrointestinal; *MI* = myocardial infarction; *PE* = pulmonary embolism. Created in BioRender. Gigliotti, B. (2025) https://BioRender.com/q77x231.

environment that supports the development of congestive heart failure and cardiogenic shock, which may be refractory to vasopressor and inotropic therapy.[36,37] Decreased glomerular filtration rate,[38] decreased renal tubular sodium reabsorption,[39] and impaired free water excretion owing to elevated plasma vasopressin levels,[40] which can lead to mild hyponatremia, have been observed. Due to impaired gluconeogenesis and possible concurrent adrenal insufficiency or attenuated cortisol response, hypoglycemia may also occur.[1,41] Depressed consciousness may stem from hypothermia, low or lack of T3 in cerebral tissue, hyponatremia, hypoxemia, hypercapnia, and/or decreased cerebral blood flow from depressed cardiac output.

The outward clinical manifestations of myxedema coma are tightly linked to the underlying pathophysiology. Figure 2 *A*[3,4,19,24,26,42,43] lists the various clinical features, by organ system, reported in the literature. Preceding these clinical features, patients often carry a diagnosis of primary hypothyroidism (usually due to Hashimoto thyroiditis, thyroidectomy, or post-radiation hypothyroidism)[19] and may exhibit signs (an expressionless puffy face with sparse hair, dry skin and brittle nails, macroglossia, periorbital and nonpitting edema, and delayed relaxation phase of deep tendon reflexes) and symptoms (cold intolerance, depression, constipation, headache, fatigue, dyspnea, swelling, modest weight gain, and muscle pain/weakness) of thyroid insufficiency.[44]

Diagnosis

Clinicians should suspect myxedema coma in patients with clinical and biochemical findings of hypothyroidism presenting with altered sensorium (from confusion and poor cognition to coma; *frank coma need not be present*) and hypothermia, perhaps in the setting of a precipitating illness. There is no biochemical pattern that reliably distinguishes compensated severe hypothyroidism from myxedema coma; diagnostic scoring systems have been developed to aid clinicians and researchers; however, they appear to be more sensitive than specific.[42,45] Immediate laboratory testing to solidify the diagnosis and investigate non-thyroidal precipitating causes, namely, infectious or cardiovascular in nature, as well as concurrent adrenal insufficiency should be completed. Workup includes thyroid-stimulating hormone (TSH), free thyroxine (FT4) with or without total thyroxine (T4), cortisol, complete blood count, complete metabolic panel, and, if appropriate, urinalysis with microscopy, blood and/or urine cultures, chest radiography, and electrocardiography. Fever may be blunted or masked by hypothermia, which may lead to underrecognition of sepsis.[3,46]

In recent studies, 7% (6/82) to 17% (4/23) of patients with myxedema coma have had underlying central hypothyroidism, which can obfuscate diagnosis due to the unreliability of serum TSH, and lead to more subtle clinical manifestations due to relatively higher T4 levels than primary hypothyroidism.[19,24] In cases of central hypothyroidism or accompanying nonthyroidal illness syndrome, the TSH level is inappropriately normal or low. Additional pituitary axis hormone deficiencies support the diagnosis of central hypothyroidism, whereas a pattern of low free and/or total T3 levels with low reverse T3 levels may help identify myxedema coma *with* nonthyroidal illness syndrome physiology.[2] Additionally, common drugs such as glucocorticoids, opioids, antiepileptics, amiodarone, and heparin affect thyroid function at multiple levels of the axis, or by affecting the binding of thyroid hormone to and concentration of protein carriers, or by interfering with thyroid laboratory test results.[47]

Treatment

Treatment of myxedema coma should involve interdisciplinary cooperation among emergency medicine physicians, internists, intensivists, and endocrinologists. Intensive supportive care is as vital to survival as thyroid hormone replacement and is summarized in Figure 3.[3,19,48-51] Improvements in ICU technology and expertise may be contributing to a decrease in mortality over

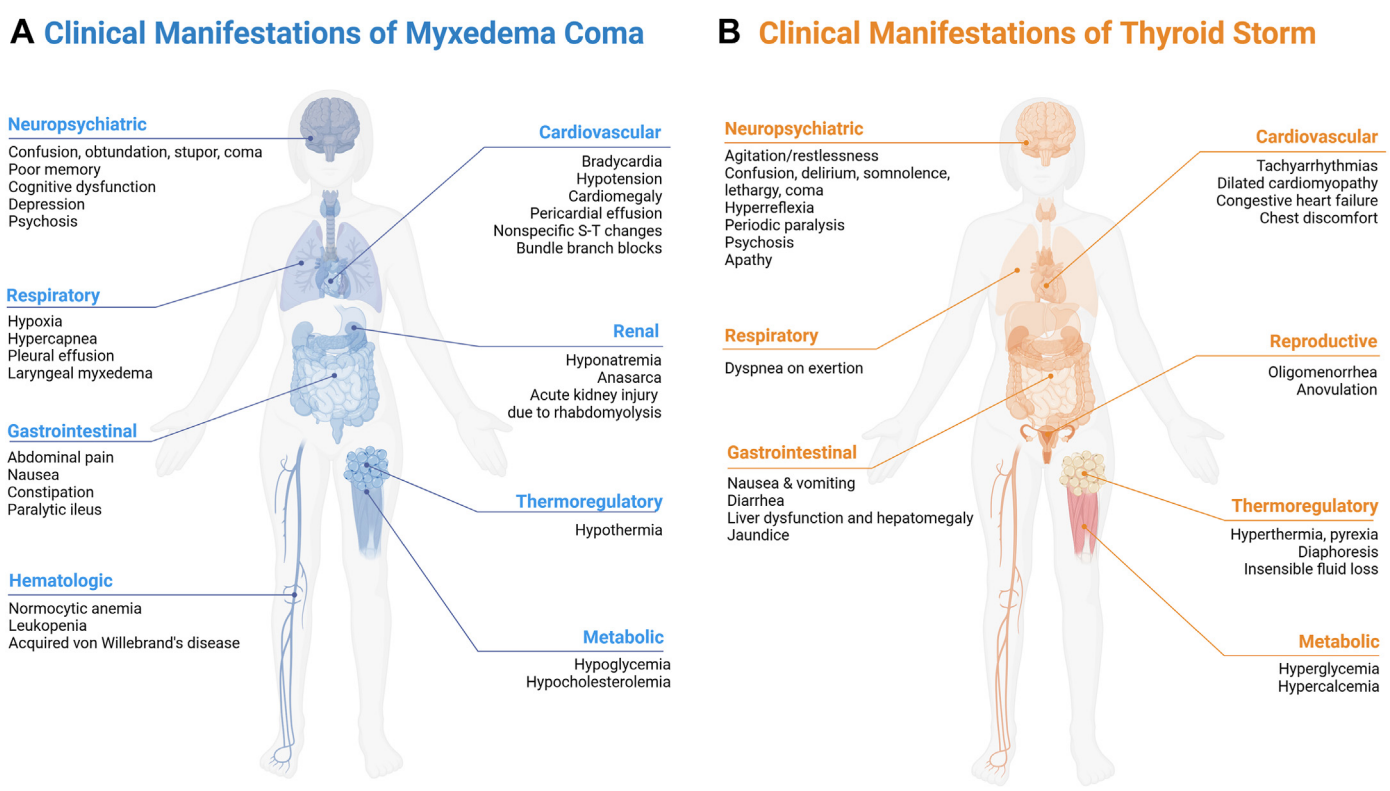

Fig. 2. Clinical manifestations of myxedema coma (*A*) and thyroid storm (*B*) that are more often seen with evidence of decompensation, compared with uncomplicated hypothyroidism and thyrotoxicosis.[3,4,19,24,26,42] N.B.1 A "normal" core body temperature is a clue for an underlying infectious trigger or that myxedema coma is not the correct diagnosis. N.B.2 Beware the muted clinical presentation of "apathetic" thyrotoxicosis, especially in elders with failure to thrive.[43] Created in BioRender. Gigliotti, B. (2025) https://BioRender.com/o43c593.

time.[23] The importance of thyroid hormone therapy was aptly stated by Wartofsky[3]: "patients with myxedema coma need thyroid hormone and die without it." However, the ideal thyroid hormone replacement regimen (oral or intravenous [IV] levothyroxine [LT4] with or without oral or IV liothyronine [LT3]) has been the topic of debate for decades. With its longer plasma half-life (approximately 7 days), LT4 therapy provides a gradual, albeit slower, onset of action with a lower risk of adverse effects, such as arrhythmias and myocardial ischemia from sudden increases in the T3 levels.[3,39,52] However, the onset of action of LT3 is rapid and can be life-saving in severe illness,[37] especially because there may be decreased peripheral conversion of T4 to T3 with severe illness.[53] Arlot et al[21] and Holvey et al[34] demonstrated that oral and IV administrations of LT4 were equally effective despite absorption concerns with the enteral route in patients with gastric atony or myxedema of the gut; later, Dutta et al[24] did not find a difference in mortality between oral and IV LT4; however, their sample size was small, which is a common limitation in this literature. After Holvey et al[34] determined an initial dose of 500 mcg of IV LT4 to replenish the depleted extrathyroidal hormone pool and account for diminished fractional daily turnover, high- versus low-dose LT4 regimens were more closely examined. Ridgway et al[41] observed that patients tolerated high doses well, although the serum T3 level after 10 days was not significantly different between high- and low-dose LT4 regimens. Rodríguez et al[23] observed a nonsignificant trend toward improved prognosis and survival in a small cohort of patients randomized to a loading dose. Bourcier et al[19] found that 43% (35/82) of patients with myxedema coma received a loading dose of LT4, which was, on average, a dose of 300 mcg. Meanwhile, Yamamoto et al[22] cautioned that doses of LT4 at ≥500 mcg/d and LT3 at ≥75 mcg/d were significantly associated with a fatal outcome, particularly in older patients, and Hylander and Rosenqvist[25] demonstrated that elevated serum T3 level following treatment with LT4 and LT3 was associated with a fatal outcome.

The most recent guidelines published by the American Thyroid Association in 2014 recommend (based on low-quality evidence) that patients with myxedema coma receive IV LT4 at a dose of 200 to 400 mcg on day 1 followed by a daily replacement dose of 1.6 mcg/kg body weight (reduced by 25% if given IV). The Task Force also noted that IV LT3 may be given in addition to LT4 at a loading dose of 5 to 20 mcg followed by a maintenance dose of 2.5 to 10 mcg every 8 hours; however, lower LT3 doses are recommended for smaller or elderly patients and those with a history of coronary artery disease or arrhythmia.[54] In the setting of a lack of consensus regarding the role of LT3, the authors' practice has been to add IV LT3 in guideline-recommended doses if the patient is critically ill, for example, requiring increasing hemodynamic and/or ventilatory support and at risk of imminent mortality in the first few days after presentation. The physiologic rationale for this approach is supported by Ladenson et al[55] who demonstrated that it takes 4 to 6 days of treatment with LT4 in overt hypothyroidism for T3 levels to normalize.

Thyroid Storm

Pathogenesis and Clinical Features

Patients who develop thyroid storm most commonly (>95% in a sample)[6] have underlying Graves disease; however, amiodarone-induced thyroiditis, toxic solitary adenoma, toxic multinodular goiter, and autoimmune thyroiditis are other reported causes.[9] Notably, although one study showed a significantly higher

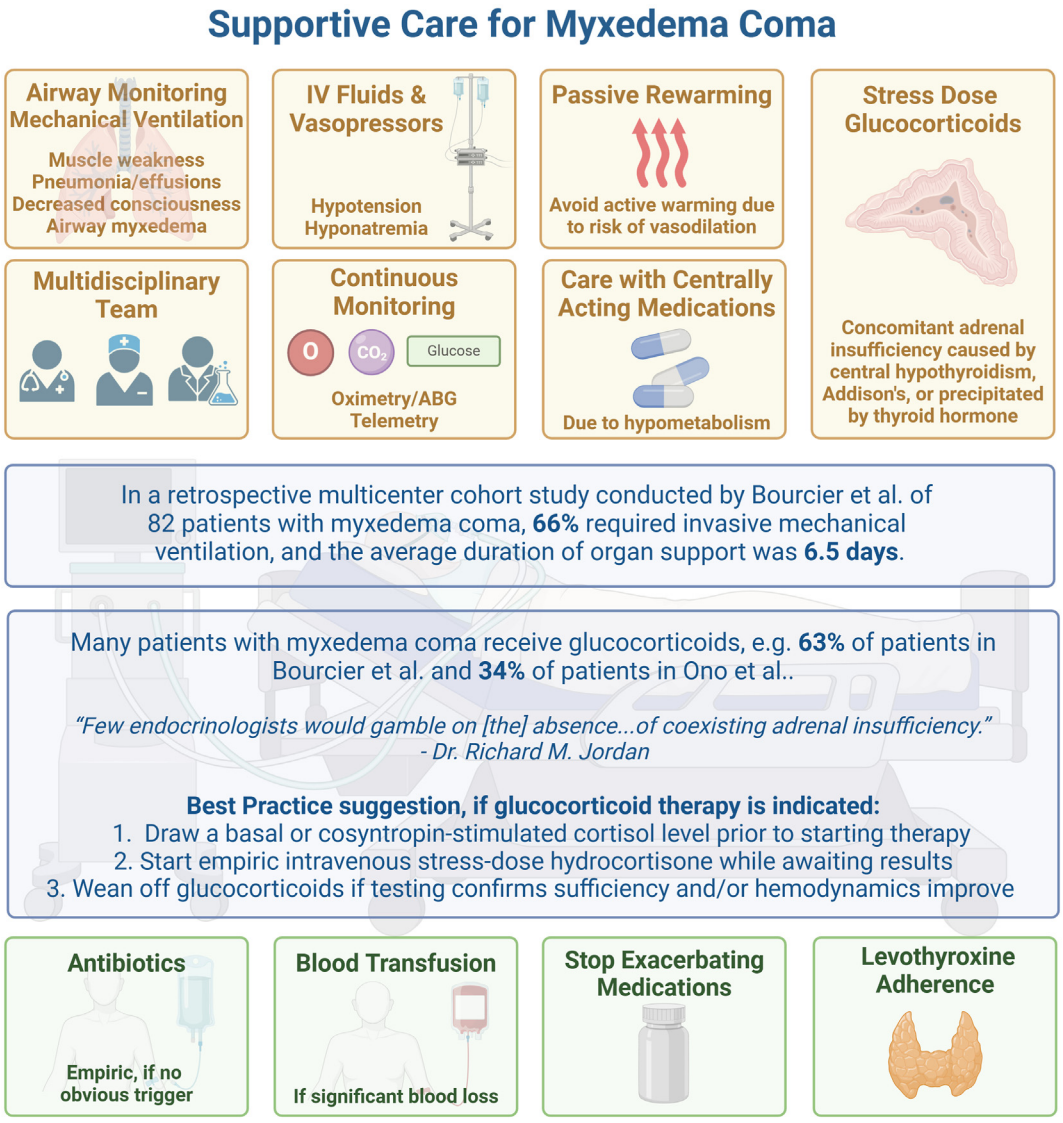
Supportive Care for Myxedema Coma
Airway Monitoring Mechanical Ventilation
Muscle weakness
Pneumonia/effusions
Decreased consciousness
Airway myxedema
IV Fluids & Vasopressors
Hypotension
Hyponatremia
Passive Rewarming
Avoid active warming due to risk of vasodilation
Stress Dose Glucocorticoids
Concomitant adrenal insufficiency caused by central hypothyroidism, Addison's, or precipitated by thyroid hormone
Multidisciplinary Team
Continuous Monitoring
O
CO2
Glucose
Oximetry/ABG
Telemetry
Care with Centrally Acting Medications
Due to hypometabolism
In a retrospective multicenter cohort study conducted by Bourcier et al. of 82 patients with myxedema coma, 66% required invasive mechanical ventilation, and the average duration of organ support was 6.5 days.
Many patients with myxedema coma receive glucocorticoids, e.g. 63% of patients in Bourcier et al. and 34% of patients in Ono et al..
"Few endocrinologists would gamble on [the] absence...of coexisting adrenal insufficiency."
- Dr. Richard M. Jordan
Best Practice suggestion, if glucocorticoid therapy is indicated:
1. Draw a basal or cosyntropin-stimulated cortisol level prior to starting therapy
2. Start empiric intravenous stress-dose hydrocortisone while awaiting results
3. Wean off glucocorticoids if testing confirms sufficiency and/or hemodynamics improve
Antibiotics
Empiric, if no obvious trigger
Blood Transfusion
If significant blood loss
Stop Exacerbating Medications
Levothyroxine Adherence

Fig. 3. Summary of supportive care interventions in the treatment of myxedema coma.[3,19,48-51] *ABG* = arterial blood gas; *IV* = intravenous. Created in BioRender. Gigliotti, B. (2025) https://BioRender.com/l43l865.

dialyzable fraction of total T4 and FT4 in (6) patients with thyroid storm than levels in patients with uncomplicated thyrotoxicosis,[56] absolute levels of serum FT4 and free T3 do not appear to distinguish compensated thyrotoxicosis from thyroid storm.[6] Many of the clinical features demonstrate a phenotype of enhanced responsiveness to β-adrenergic stimulation, which is enigmatic because there are no increase in circulating levels of catecholamines,[57,58] only modest increases in receptor number, and a reduction in central sympathetic nervous system activity.[59]

Because Graves disease is the most common underlying disease in thyroid storm, manifestations such as goiter with thrills/bruits; heat intolerance and profuse diaphoresis; irritability, anxiety, and restlessness; a fine tremor and brisk reflexes; muscle weakness and, rarely, periodic paralysis; tachycardia and palpitations; and nausea, vomiting, and abdominal pain are common.[60] High fevers, central nervous system symptoms (altered sensorium or mental aberration), congestive heart failure, atrial tachyarrhythmias, intensified gastrointestinal symptoms, or jaundice with liver dysfunction distinguish thyroid storm from uncomplicated thyrotoxicosis.[6] Figure 2 *B* lists the various clinical features of thyroid storm complied from the literature.[4,26]

Diagnosis

The clinical syndrome of thyroid storm should be suspected in patients with thyrotoxicosis (elevated FT4 or free T3 levels) and evidence of multi-organ decompensation (specifically, hyperthermia and altered mentation) following a precipitating event. Laboratory evaluation (complete metabolic panel and complete blood count) may reveal leukocytosis, elevated transaminase levels, hyperbilirubinemia, hypercalcemia, and hyperglycemia.[5] Pathognomonic clinical features of Graves disease (ie, exophthalmos, pretibial myxedema, and acropachy) quickly confirm an underlying diagnosis of Graves disease.[11] Thyroid ultrasound with Doppler flow can help quickly albeit subjectively clarify the etiology of thyrotoxicosis, for example, distinguishing thyroid hyperactivity from destructive thyroiditis, and is quicker than an inpatient iodine-123 or technetium uptake and scan or TSH receptor antibodies.[28,61,62]

Diagnostic criteria have been developed to aid in the diagnosis of thyroid storm, including the Burch-Wartofsky Point Scale (BWPS), a quantitative, empirically derived scoring system, as well as a framework by the Japanese Thyroid Association (JTA). The

BWPS, introduced in 1993 after application to 61 cases in the literature, assigns points for varying degrees of dysfunction in the thermoregulatory, central nervous, gastrointestinal-hepatic, and cardiovascular systems as well as presence or absence of a precipitant.[26] A score of ≥45 is highly suggestive of thyroid storm, that of 25 to 44 is categorized as impending storm, and that of <25 is unlikely to be thyroid storm. A decade later, the JTA formulated new diagnostic criteria from literature review and a large multicenter case series. With thyrotoxicosis as a prerequisite, cases of "suspected" and "definite" thyroid storm are diagnosed when patients display varying combinations of central nervous system manifestations, fever, tachycardia, congestive heart failure, and gastrointestinal-hepatic manifestations.[6] At least 3 retrospective studies[6,10,62] and 1 prospective study[16] have compared the BWPS and the JTA diagnostic criteria, concluding overall agreement in most cases but noting that the BWPS tends to be more sensitive, risking false positives and overtreatment, whereas the JTA diagnostic criteria are more specific and less sensitive. Recent studies have relied on the JTA diagnostic criteria to define their study populations.[9,16]

Treatment

Strategic and timely treatment to reduce circulating thyroid hormone and prevent end-organ damage has been described by others[26,61] and involves intervening at each pharmaceutically accessible step in thyroid hormone synthesis and action. Simultaneously, close hemodynamic monitoring in an ICU setting and supportive care are paramount, similar to the treatment of myxedema coma described earlier. Table 3 outlines the battery of treatment options in order of ascending severity of the patient's condition, as well the importance of supportive care. Because prevention is often said to be the best medicine, physicians should educate patients about common-sense preventive measures, including the importance of adherence to ATDs, need for prompt medical care in the event of intercurrent illness, and careful timing of elective surgery.

Thionamides (propylthiouracil [PTU], methimazole [MMI], or carbimazole, which is metabolized to MMI) inhibit thyroid peroxidase (thereby thyroid hormone synthesis) and are first-line, thyroid gland–specific treatment. The 2016 "American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and… Thyrotoxicosis" recommend PTU over MMI.[61] PTU has been traditionally favored over MMI owing to its inhibition of peripheral conversion of T4 to T3[63]; however, a recent large multicenter retrospective US-based cohort study found no significant difference in death or discharge to hospice with PTU versus MMI and concluded that ATDs could be used interchangeably.[13] Years earlier, in a large retrospective cohort study of 1324 patients with thyroid storm in Japan, 66% were treated with MMI alone compared with PTU alone or use of both agents, and there was no significant difference in mortality.[15] In a recent prospective cohort study of 110 patients with thyroid storm also in Japan, nearly all (96%) received MMI alone.[16]

ATDs are often followed by inorganic iodine, which inhibits release of T4 and T3 from the thyroid gland and transiently quells thyroid hormone synthesis via the Wolff-Chaikoff effect. Longstanding dogma dictates that iodine should be administered at least 1 hour after ATDs are administered to ensure blockade of new thyroid hormone synthesis and prevent utilization of iodine for thyroid hormone production (the Jod-Basedow phenomenon).[64] However, 2 prospective studies comparing the therapeutic and adverse effects of MMI treatment at varying doses (15 or 30 mg/d) with or without concurrent inorganic iodine in patients with untreated Graves hyperthyroidism concluded that combined

Table 3
Spectrum of Treatment Options for Patients With Thyroid Storm

Treatment targets for thyroid storm				Definitive therapy
Least aggressive → Most aggressive				Radioactive iodine ablation
Thyroid hormone synthesis and release	Thionamides: PTU and methimazole	Inorganic iodine: saturated solution of potassium iodide or Lugol's solution Lithium or amiodarone therapy	Emergent thyroidectomy	Total or near-total thyroidectomy
Peripheral T4 → T3 conversion and circulating hormone effects	Beta-blockers: Propranolol and esmolol	PTU and glucocorticoids	Cholestyramine therapy	Plasmapheresis
Supportive care and resuscitation				
ICU setting with hemodynamic monitoring	Hyperthermia Acetaminophen Cooling techniques—ice packs, cooling blankets, and alcohol sponges	Hypovolemia Aggressive IV fluid replenishment with 5%-10% dextrose *except* in patients with heart failure	Cardiovascular complications Very short-acting selective beta-1-selective blocker (esmolol) preferred	Decreased adrenal reserve Stress dose glucocorticoids: hydrocortisone or dexamethasone

Abbreviations: ICU = intensive care unit; IV = intravenous; PTU = propylthiouracil; T4 = thyroxine; T3 = triiodothyronine.

treatment with MMI and iodine decreased the thyroid hormone levels significantly faster than MMI alone and without exacerbation of thyrotoxicosis.[65,66] As such, the 2016 JTA and Japan Endocrine Society guidelines for the management of thyroid storm recommend that iodine be administered simultaneously with ATDs to patients with thyroid storm caused by Graves disease,[67] and in a subsequent prospective study, the fatality rate tended to be lower in the group with iodine administration within 1 hour after ATD administration, as opposed to more than 1 hour after ATD administration.[16] Iodine-induced worsening of thyrotoxicosis is likely restricted to cases in which hyperthyroidism is due to autonomous thyroid nodules.[68]

Beta-adrenergic receptor blockers (β-blockers) have long been frontline agents for most patients in thyroid storm to antagonize the hyperadrenergic manifestations of thyrotoxicosis. β-blockers, whether β1-selective or nonselective, are widely used and rapidly ameliorate symptoms of hyperthyroidism and many of the hemodynamic consequences of increased β-adrenergic tone.[69,70] However, a recent systematic review (of case reports) focusing on the small proportion of patients who develop cardiogenic shock due to thyrotoxicosis or thyroid storm suggests careful and measured use. Modarresi et al[71] caution against use of β-blockers (even ultrashort-acting variants such as esmolol) in those at risk of or actively developing cardiogenic shock, demonstrating a role for plasmapheresis and cardiac mechanical support (Impella, intra-aortic balloon pump, or extracorporeal mechanical ventilation). Cardiogenic shock occurred within 48 hours in 38% (35/92) of patients with thyroid storm admitted to multiple ICUs across France, and its presence was significantly associated with mortality.[9]

Because sustained, severe thyrotoxicosis may be associated with inadequate adrenocortical reserve, empiric administration of glucocorticoids at stress doses is recommended in thyroid storm to prevent relative adrenal insufficiency.[61,72] Additionally, glucocorticoids reduce peripheral conversion of T4 to T3.[73] However, a retrospective cohort study relying on the Japanese national administrative claims database (n = 811) found no significant improvement in the in-hospital mortality of patients with thyroid storm treated with glucocorticoids compared with those treated without glucocorticoids.[74] In opposition, Furukawa et al[16] found that patients who received insufficient doses of glucocorticoids had poorer prognosis than those who received sufficient doses, although glucocorticoids were often reserved for the sickest patients. Both the American and Japanese guidelines addressing thyroid storm management recommend use of glucocorticoids.[61,67]

Conclusion

Myxedema coma and thyroid storm are life-threatening conditions at opposing ends of the thyroid function spectrum. Affected patients deserve prompt recognition and effective treatment to restore thyroid hormone balance and ensure survival.

Disclosure

The authors have no conflicts of interest to disclose.

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